From Dr. Niranjan

1: *Mol Ther* 2000 Jan;1(1):71-81 Related Articles, Books, LinkOut

Connexin 43-enhanced suicide gene therapy using herpesviral vectors.

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Tumor cell transduction with the herpes simplex virus (HSV) thymidine kinase (tk) gene and treatment with ganciclovir (GCV) is a widely studied cancer gene therapy. Connexin (Cx)-dependent gap junctions between cells facilitate the intercellular spread of TK-activated GCV, thereby creating a bystander effect that improves tumor cell killing. However, tumor cells often have reduced connexin expression, thus thwarting bystander killing and the effectiveness of TK/GCV gene therapy. To improve the effectiveness of this therapy, we compared an HSV vector (TOCX) expressing Cx43 in addition to TK with an isogenic tk vector (TOZ.1) for their abilities to induce bystander killing of Cx-positive U-87 MG human glioblastoma cells and Cx-negative L929 fibrosarcoma cells in vitro and in vivo. The results showed that low-multiplicity infection of U-87 MG cells with TOCX only minimally increased GCV-mediated cell death compared with infection by TOZ.1, consistent with the endogenous level of Cx in these cells. In contrast, bystander killing of L929 cells was markedly enhanced by vector-mediated expression of Cx. In vivo experiments in which U-87 MG cells were preinfected at low multiplicity and injected into the flanks of nude mice showed complete cures of all animals in the TOCX group following GCV treatment, whereas untreated animals uniformly formed fatal tumors. TOCX injection into U-87 MG intradermal and intracranial tumors resulted in prolonged survival of the host animals in a GCV-dependent manner. Together, these results suggest that the combination of TK and Cx may be beneficial for the treatment of human glioblastoma.

PMID: 10933914